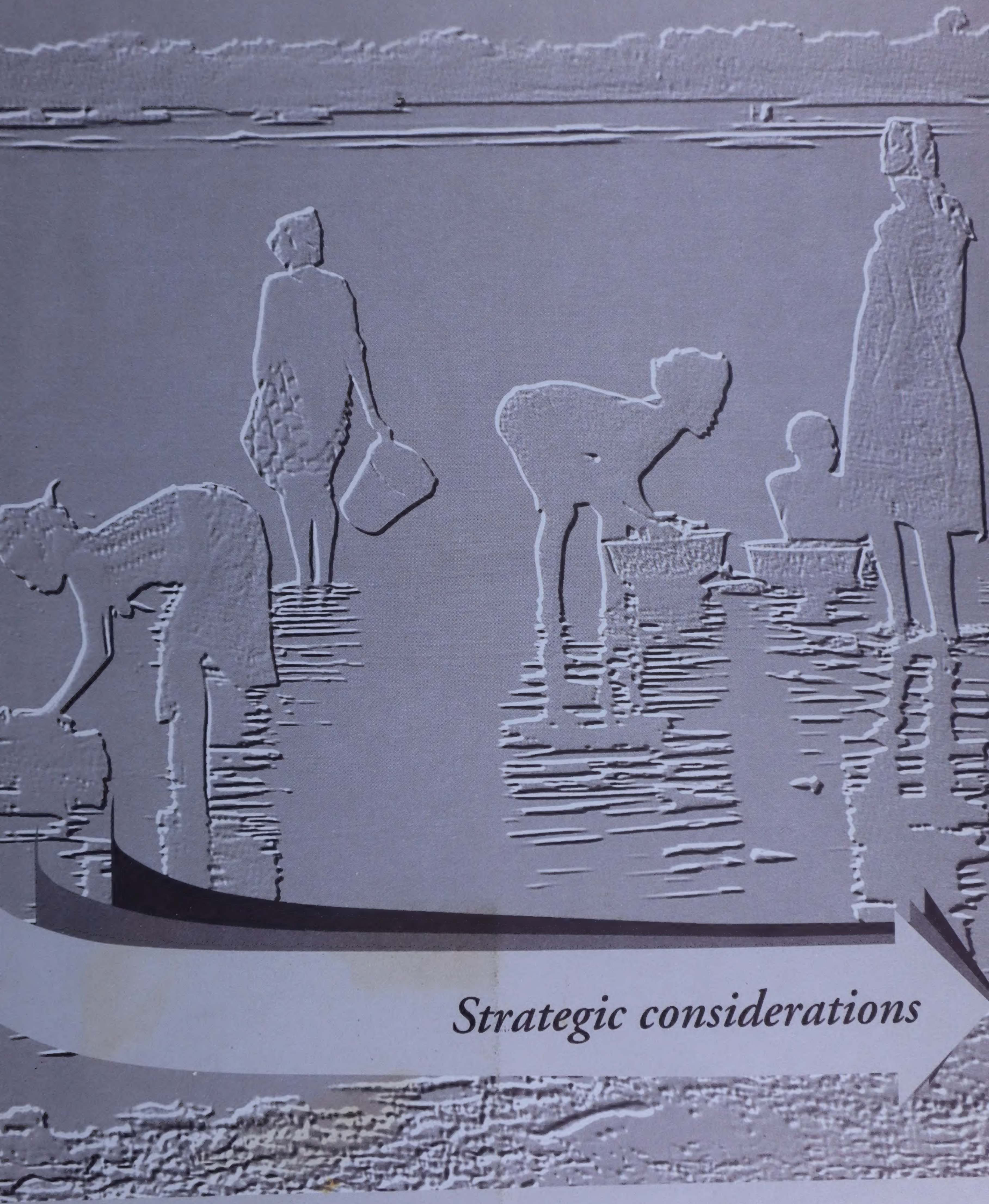
TDR towards the Year 2000



Strategic considerations

TDR

UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases

TDR Towards the Year 2000

Strategic considerations

WORKING DOCUMENT FOR DISCUSSION AT JCB-16, JUNE 1993

UNDP/WORLD BANK/WHO
Special Programme for Research and Training in Tropical Diseases (TDR)

WORKING DOCUMENT FOR DISCUSSION AT JCB-16, JUNE 1993

TABLE OF CONTENTS

PREFACE

The growth of any living organism is rooted in its ability to learn from the past and adapt to change.

TDR, to the extent that it is alive and responsive to its surroundings, is no exception. Over the past five years, TDR began to undergo a series of experimental changes in focus and structure in response to a new appreciation of its role and of the scope of its mandate. Over the past two years, it has undertaken a comprehensive critical reappraisal of the way its activities are organized. This review process has involved experts from many areas of science, management and development. It has culminated in a series of recommendations that should make TDR better equipped to achieve its objectives.

The present document outlines this period of "growth by trial-and-error" and attempts to place it in the historical perspective of TDR's early years. It also touches on the changing world to which TDR must relate in a continuous process of adaptation and tries to identify the specific roles TDR is best suited to play among the many "agents of change" on the development scene.

If the recommendations are approved by the June 1993 session of the Joint Coordinating Board, this document could serve as an up-to-date introduction to TDR. It has therefore been written in a style accessible, it is hoped, to readers interested in tropical diseases but not necessarily familiar with TDR. (More complete, official documentation relating to the review process is available on request to the TDR secretariat.)

"Up-to-date", of course, will soon be "out-of-date". Yet, in the flow of time we must occasionally stop and take stock. To emerge perhaps into a new time, when, as the novelist John Le Carré recently pointed out, "... we are are shorn of all our old excuses for not addressing the real problems of the earth...Yet, we have never been so free. We no longer need to clip the wings of our humanity. It's time we flew....[1]"

Tore Godal

Tore Godal
Director, TDR

[1]from a speech to the Boston Bar Association delivered 3 May, 1993

PREFACE

The growth of any living organism is rooted in its ability to learn from the past and adapt to change.

TDR, to the extent that it is alive and responsive to its surroundings, is no exception. Over the past five years, TDR began to undergo a series of experimental changes in focus and structure in response to a new appreciation of its role and of the scope of its mandate. Over the past two years, it has undertaken a comprehensive critical appraisal of the way its activities are organized. This review process has involved experts from many areas of science, management and development. It has culminated in a series of recommendations that should make TDR better equipped to achieve its objectives.

The present document outlines this period of "growth by trial-and-error" and attempts to place it in the historical perspective of TDR's early years. It also looks to the changing world to which TDR must relate in a continuous process of adaptation and tries to identify the specific roles TDR is best suited to play among the many "agents of change" of the development scene.

If the recommendations are approved by the June 1993 session of the Joint Coordinating Board, this document could serve as an up-to-date introduction to TDR. It has therefore been written in a style accessible to a larger readership interested in tropical diseases but not necessarily familiar with TDR. (More complete, official documentation relating to the review process is available on request to the TDR secretariat.)

"Up-to-date", of course, will soon be "out-of-date". Yet, in the flow of time we must occasionally stop and take stock. To emerge perhaps into a new time, when, as the novelist John Le Carré recently pointed out, "...we are short of all our old enemies but not addressing the real problems of the earth... Yet, we have never been so free. We no longer need to clip the wings of our humanity, it's time we flew..."

Tore Godal

Director, TDR

[illegible]

SECTION 1: TDR'S EARLY YEARS

The "global village" movement

The UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) came into existence in 1975 at a time when *planetary awareness* was gathering momentum and *development* was taking off as a political science amid much talk of a *North-South dialogue.* As this movement grew, the continued suffering of tropical populations from diseases long departed from the developed world was seen ever more acutely in the West as an unacceptable anachronism and an example of inequity at its worst. Therefore, when about this time biomedical science began breaking new ground in several disciplines, notably genetics, molecular biology and immunology, the development community turned to scientific research for solutions to the problems of controlling the tropical diseases.

TDR was given a two-fold mandate: to enlist the new-found power of science in a highly focused search for these solutions and to enable the developing countries affected by the diseases to join in the search (see Box 1).

> **Box 1:**
> **TDR's double mandate**
>
> TDR was set up in 1975 to:
>
> - develop new methods of preventing, diagnosing and treating selected tropical diseases, methods that would be applicable, acceptable and affordable by developing countries, require minimal skills or supervision and be readily integrated into the health services of these countries;
> - strengthen – through training in biomedical and social sciences and through support to institutions – the capability of developing countries to undertake the research required to develop these new disease control technologies.

Compartments and components

In attempting to fulfil this mandate, TDR has always supported the full spectrum of research, from basic research to product research and development to applied field research. Initially, the emphasis was more on basic research, undertaken to provide basic knowledge about tropical diseases as a prerequisite to identifying technological solutions to their control. For this purpose, the diseases were considered as distinct entities: TDR's research funding activities were organized under separate *scientific working groups,* managed by *steering committees,* one for each of the diseases – selected as research targets on the basis of their public health impact, namely, malaria, schistosomiasis, filariasis (elephantiasis and river blindness), African trypanosomiasis (sleeping sickness), Chagas disease, leishmaniasis and leprosy.

Even in those early days, steering committees were established for research on topics common to several or all of the diseases – biological control of vectors, epidemiology, social

and economic research, and the biomedical sciences. All but the steering committee for biomedical sciences have survived in one form or another to the present day. In addition, a special steering committee, the Research Strengthening Group, was set up to oversee TDR's commitment to developing country research and manage TDR's *research capability strengthening* activities.

A productive beginning

By and large, this set-up has worked: 78 different products – drugs, vaccines, diagnostic techniques and vector control agents – have emerged or are emerging from research funded wholly or partly by TDR (Annex 1). Of these, 24 are being used by disease control programmes, 35 are in clinical or field trials and 19 are in preclinical development. In addition to these tangible products, research backed by TDR has produced a number of solutions and insights related to disease control problems (Boxes 2 and 3).

The extent to which TDR is fulfilling its mandate to strengthen the research potential of developing countries is more difficult to quantify, since there is no comprehensive set of indicators of a country's research capability. In terms of input, at least, by the end of 1992, TDR had spent US$85.8 million in 70 developing countries on 1,339 training grants awarded to 1,085 people (including grants for 14 Master's level training programmes in 12 countries) and on 188 grants to 140 institutions in 46 countries.

Box 2: Some products and solutions resulting from research supported by TDR

- early warning of the spread of resistance to dapsone among leprosy patients throughout the world
- development of multidrug therapy for leprosy
- clinical development of a new drug, ivermectin, for the treatment of onchocerciasis and lymphatic filariasis
- a new regimen for antimonial therapy of visceral leishmaniasis
- multicentre trials to determine whether the use of impregnated mosquito nets can reduce overall and malaria-related child mortality in Africa
- pioneering research on leprosy vaccines through the creation of a unique worldwide basic and clinical research network
- mapping of the prevalence of leishmaniasis
- clinical development of the new drug eflornithine and its analogues for the treatment of African trypanosomiasis, and field trials of a diagnostic test – the Card Agglutination Test for Trypanosomiasis – and of tsetse fly traps
- international, multicentre trials of new antimalarial drugs
- research on vaccines against malaria, schistosomiasis and leishmaniasis
- setting up of a network of Chagas disease research centres in developing countries, from whose work a better understanding has emerged of the pathogenesis, immunology and social aspects of the disease, and better control of its insect vector
- development of a biological vector control agent, *Bacillus thuringiensis* H-14, now used extensively in the control of onchocerciasis

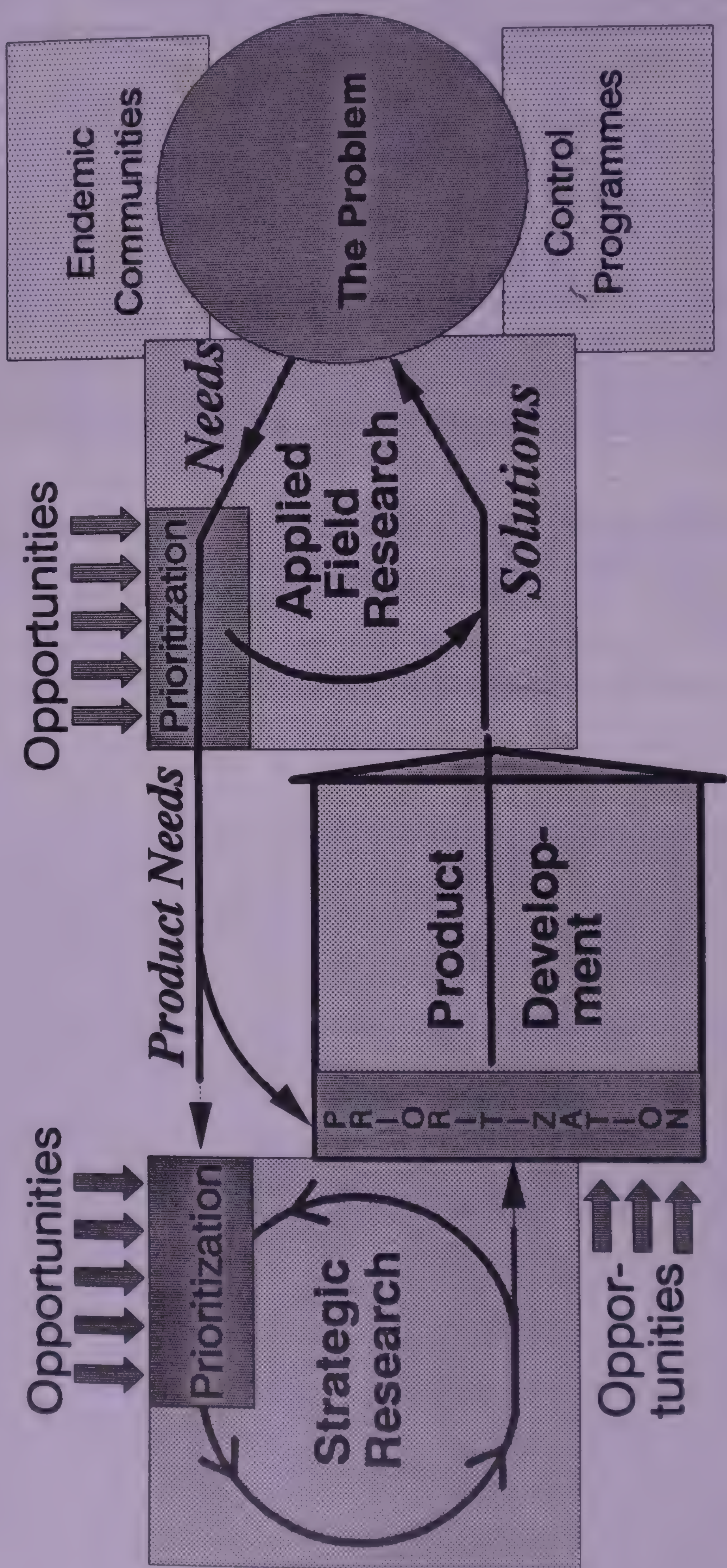
BOX 3: A sampling of topics explored through socioeconomic, epidemiological and field research studies backed by TDR

TDR is making increasing use of highly focused field research to find ways of making the products of research more effective for disease control. Examples:

- how to rapidly identify communities heavily infected with onchocerciasis in preparation for mass administration of ivermectin
- the role of gender in tropical disease
- the potential role of children of school age in determining the prevalence of disease in a community and in disseminating information about health
- improving the use of antimalarial drugs in areas of South-East Asia where resistance to these drugs is widespread
- the impact of health financing systems on treatment seeking
- a multicentre study in four African countries on whether the use of insecticide-impregnated mosquito nets can lower child mortality
- a study on the feasibility of concurrent diagnosis and treatment of acute respiratory infections and malaria in children

Another poorly quantifiable but significant achievement generally ascribed to TDR is that of having played a major role in bringing tropical diseases to the attention of the world's scientific community.

Fig. 1
Phases in Tropical Disease Research



SECTION 2: THE SCENE CHANGES

By the late 1980s, three concurrent trends set in motion a process that laid the basis for a change in TDR's structure and working style:

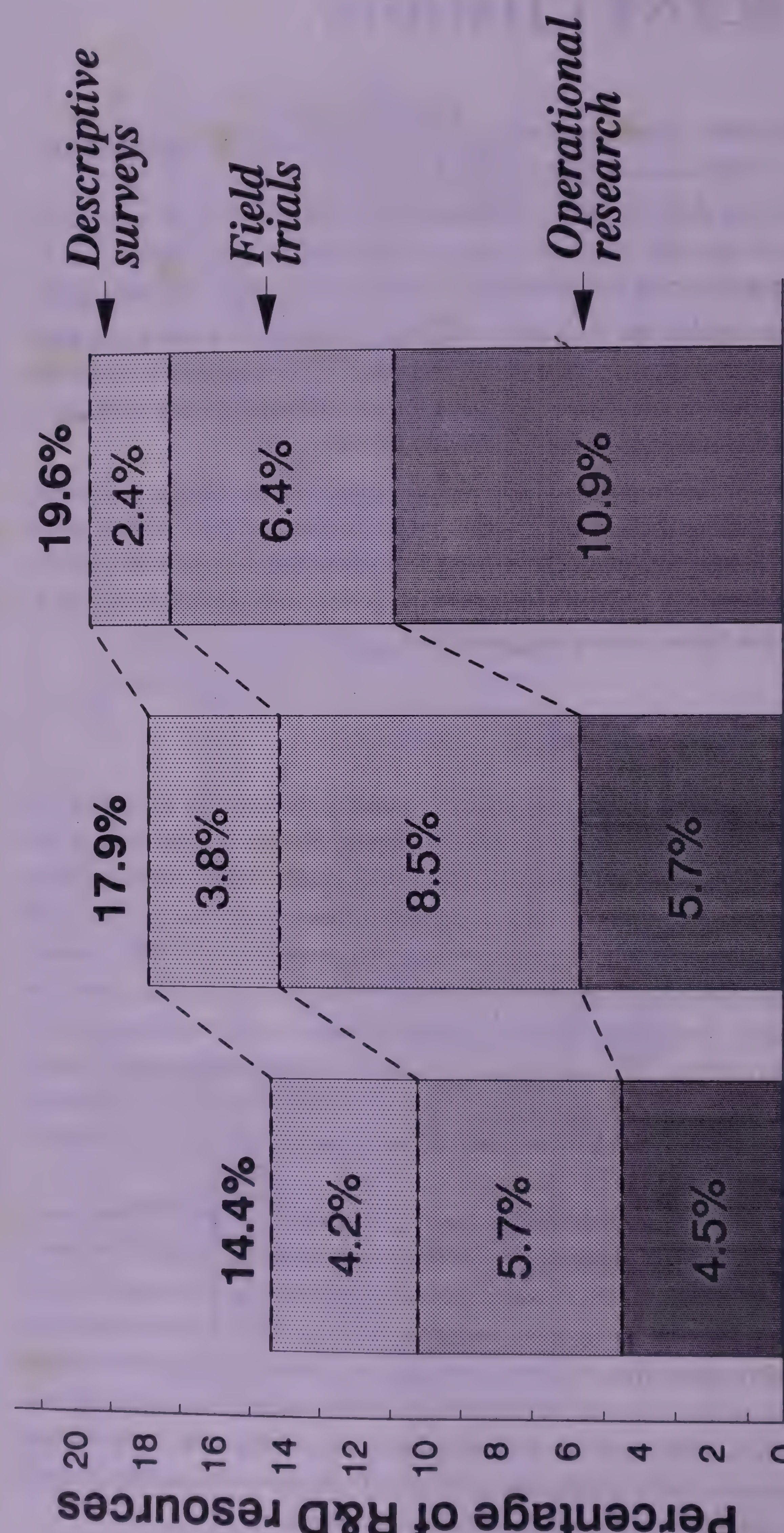
- it was becoming clear that when a new disease control tool comes off the research and development assembly line, further research is required to ensure that it will be correctly applied and will have an impact on disease (see below, *From the field and back*);
- it was becoming clear that the burden of the diseases, taken as a whole and considered in their social settings, was as heavy as ever and likely to become heavier (see Box 4); moreover, the diseases themselves were seen to present a far more complex set of targets than previously suspected (see below, *The plot thickens*, p. 10);
- competition for development funding was increasing, with a consequently stronger demand by funding agencies and governments for a demonstration of effective use of resources – namely, impact on disease of the research funded through these resources – and a more stringent selection of only those research options most likely to have such an impact (see below, *Making every penny count*, p. 11).

From the field and back

The very success of TDR's early efforts to mobilize the scientific community in devising new tools and tactics for controlling tropical diseases brought with it the realization that, as the 1987-88 external review of TDR noted, TDR's work would have to include "the demonstration of the utility of the tools in their intended setting of use...and the initial exploration of the most appropriate means of their application". TDR's mandate would, therefore, have to edge closer to the borderline between research and control. Its work would have to concentrate less on unravelling the intricacies of the diseases and their causative agents and more on ensuring the applicability of the new tools to field use and on a search for field solutions to problems of disease control. The *field* would become TDR's starting point – where research needs are defined – and end-point, where its research products are used (Fig. 1).

With this shift in focus to the field and with TDR-sponsored research chosen more stringently for its likely contribution to disease control and its likely impact on the disease burden, a new definition of TDR's research spectrum was beginning to take shape: at one end, *basic research* was becoming more *strategically* aimed at high-priority targets (and began to be called *strategic research*); at the other, field research was becoming more *applied* to disease control (and came to be termed *applied field research*); and spanning and interacting with the whole spectrum was *product research and development*, to which a new *Product Development Unit* would provide expert input; finally, *Research Capability Strengthening* was brought more in line with TDR's new field orientation.

Fig. 2
Trends in the distribution of TDR's applied field research resources



This new conceptual framework set the scene for a number of experimental changes in the management of TDR's activities:

- On the *basic research* end of the spectrum, in 1985, TDR disbanded its biomedical sciences steering committee, whose work did not have a direct enough bearing on disease control. It then began to weed from the priorities of the individual disease-oriented steering committees topics (such as rational design of antifilariasis drugs and experimental models) with too weak a potential for impact on disease control to be called strategic research.
- In *field research*, epidemiological studies began to turn from descriptive disease surveys and the identification of risk factors to focus increasingly on field trials of new disease control tools and strategies (Fig. 2). An Epidemiology and Field Research Support Unit was created to feed into and draw on the expertise of other TDR steering committees working on "field-ready" tools (such as ivermectin for onchocerciasis and lymphatic filariasis) so as to ensure the quickest, most cost-effective introduction of the most promising disease control tools into local disease control operations. At the same time, TDR's social and economic research activities began to move away from descriptive studies of the social, cultural and economic factors affecting communities to concentrate more on how control tools and strategies might be designed so as to meet the needs of communities, as expressed by the communities, and so be more likely to be accepted, used and effective. Backed by TDR's organizational and financial support, social scientists, working closely with biomedical researchers, epidemiologists, parasitologists, clinicians and public health experts, started to work directly with national disease control programmes (on malaria in Thailand and Chagas disease in Argentina and Venezuela, for example) in exploring ways of strengthening the relationship between these programmes and the people they were set up to serve. Social scientists supported by TDR began to explore how to obtain usable results more quickly from their field research (such as using the school system to identify communities at risk of urinary schistosomiasis). And studies on population groups vulnerable to disease, notably women and migrants (Box 4), gave social scientists an opportunity to identify some of the social inequities contributing to ill health.
- In *product research and development*, TDR set up in 1990 a Product Development Unit to draw on expertise for different stages of the product development process – toxicity testing, formulation, production and packaging, intellectual property rights and preparation for registration – wherever suitable partners could be found. The following year, TDR created a Steering Committee on Integrated Chemotherapy for African Trypanosomiasis, Chagas Disease and Leishmaniasis (I-CHEM) to speed the development of drugs for these diseases. At about the same time, TDR linked up with the Onchocerciasis Control Programme in West Africa (OCP) in a project (called MACROFIL) to find a drug capable of killing adult filarial worms (macrofilariae). By and large, TDR's need to enter what has traditionally been the pharmaceutical industry's bailiwick stemmed from the industry's declining interest in developing products for tropical diseases. As it turns out, TDR's expertise and resources for organizing clinical trials in developing countries and its consequent ability to reduce overall product development costs have formed the basis for several collaborative projects with pharmaceutical firms.

BOX 4:
The disease burden, a largely *unchanging* scene

The diseases

The tropical diseases that justified the creation of TDR 18 years ago constitute just as heavy a burden on the people of the developing countries now as they did then. If anything, with an additional 1.5 billion people living in these countries, the burden as a whole, as measured by estimated numbers of people directly or indirectly affected (see Table below), is probably even greater—more than half the world's population at risk of infection in over 100 countries, at least 500 million people infected at any one time by at least one of the diseases and at least two million deaths a year. And 17 years from now, in 2010, the situation could be much worse, with the death rate expected to double if radical solutions are not found to control the diseases. For all but three of them—leprosy, Chagas disease and onchocerciasis, which are likely to decline in prevalence through effective control—the prospects are grim, with the spread of parasite resistance to drugs and the increasingly frequent disruption of disease control programmes through civil turmoil, economic devastation and massive population movements.

Perhaps the most critical determinant of future trends in the tropical disease burden is the growth in the world's population—likely to rise over the next two decades from the current 5.4 to 7.1 billion: about 90 percent of this population increase is expected to occur in developing countries (50 percent in Africa alone)[2], where resources to treat and prevent the diseases are declining, where 1.2 billion people live in absolute poverty, where 14 million children die every year before the age of five[3], and where the tropical diseases will, if nothing stops them, add their share of pain, deformity and death to an already vulnerable population. For malaria alone, population growth, even without an increase in mortality rate, could double the number of deaths to 2 million a year (Fig. 3).

Another factor favouring the spread of tropical infections, especially malaria, and complicating attempts to combat it, is the increase in numbers of migrants among people from developing countries, currently estimated at about 75 million each year[3], among them 17 million refugees[4] living in sometimes precarious sanitary conditions. Settlers or workers previously unexposed to tropical diseases may move to areas where their lack of immunity puts them at high risk of infection with locally prevalent parasites: gold miners and settlers in Brazil's Amazon region and gem workers in Cambodia, for example, are particularly vulnerable to malaria; soldiers brought to the Gulf area during the recent war have been exposed to leishmaniasis; and in the Sahel migrant labourers with endemic urinary schistosomiasis have contaminated waterways on their migration routes. Economic development can also bring with it an increased risk of tropical infection (such as schistosomiasis and malaria in water resource schemes in Senegal and Sri Lanka, and reforestation projects in South-East Asia).

Estimates of the statistical burden of the diseases targeted by TDR's activities

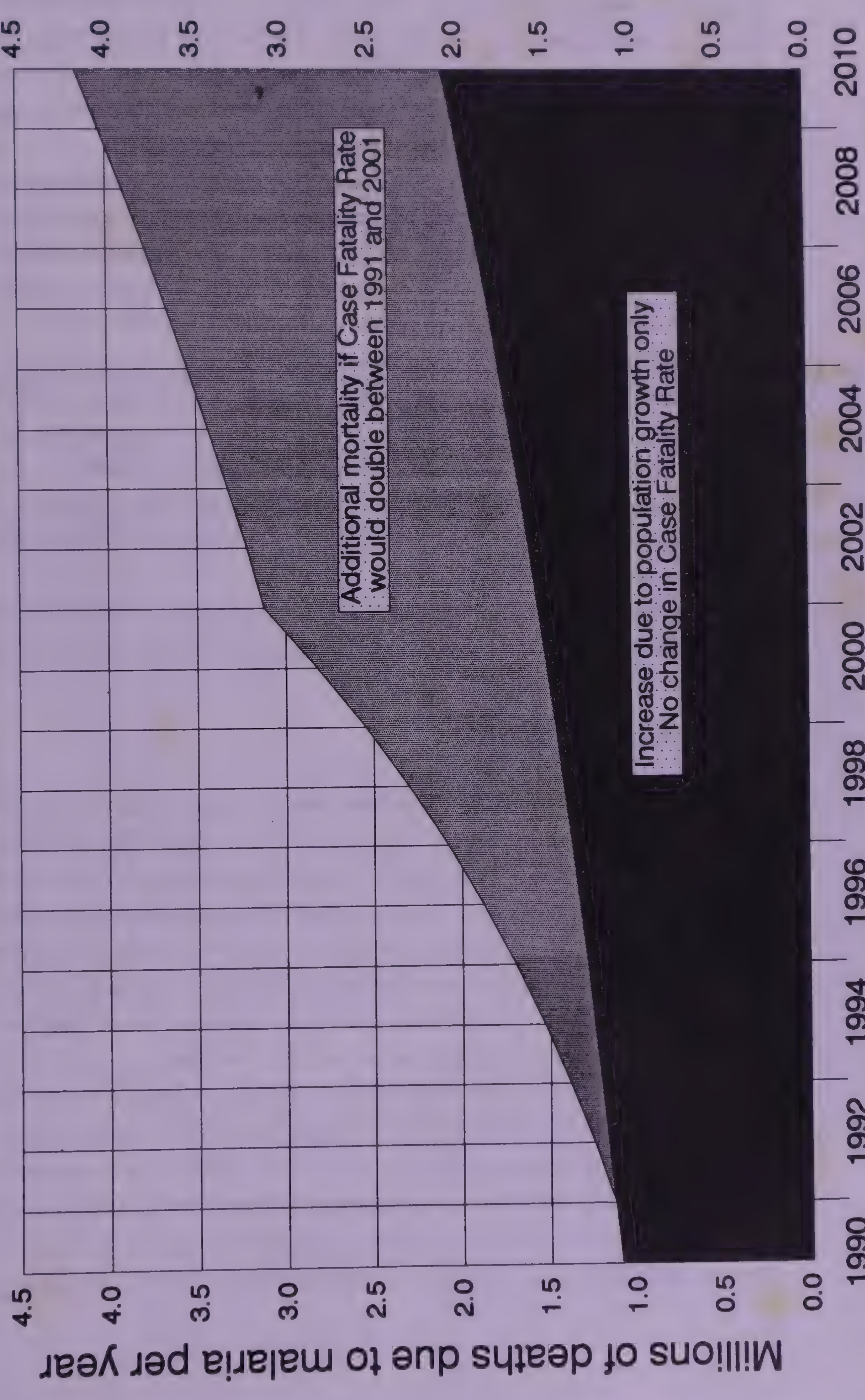
Disease	No. of countries affected	Est'd (min.) nos. of people at risk (millions)	Est'd (min.) nos. infected (millions)	% infected of those at risk
Malaria	103	2,100	300.0	14.3
Schistosomiasis	74	600	200.0	33.3
Lymphatic filariasis	76	905	78.6	8.7
Onchocerciasis	34	90	17.6	19.6
African trypanosomiasis	36	50	0.1	0.2
Chagas disease	21	90	17.0	18.9
Leishmaniasis	80	350	12.0	3.4
Leprosy	121	1,600	100.0	6.3

[2]World Population Projections, 1989-90, World Bank. Increased mortality from AIDS could reduce population growth rates (by up to 1 percentage point in Africa, according to the World Bank's World Development Report 1992), but may at the same time slow the decline in fertility rates, leaving doubt as to the net effect on population growth.

[3]Human Development Report 1992, UNDP

[4]*Our planet, our health*, Report of the WHO Commission on Health and Environment, 1992, WHO

Fig. 3
Worst case scenario for malaria mortality



- *Research capability strengthening* had begun, in the late 1980s, to respond to the "call of the field" that was beginning to transform TDR's basic and field research activities. There was less emphasis on numbers of institutions strengthened and scientists trained and more on how they could contribute to – as well as learn from – ongoing research applied to real-life disease control problems. In the process, the Research Strengthening Group was beginning to work more closely with TDR's research and development steering committees – to use, for example, institutions being strengthened and scientists being trained as resources for research and development projects, and vice versa.

In many ways, it was TDR's research capability strengthening work that most visibly reflected the multifaceted, network or *matrix* paradigm that was sweeping over development research at the time (see below, *The plot thickens*). New *programme-based grants* were created to encourage institutions in developing countries to conduct multidisciplinary research that would bring to disease control the benefits of scientific progress. *Joint TDR-Rockefeller Foundation grants* fostered North-South twinning arrangements between research groups or institutions. And a programme of *field linkages* – Field Links for Intervention and Control Studies (FIELDLINCS) – was set up to bring together scientists from different disciplines, at different levels of experience, from different cultural and scientific backgrounds, to work on problems related to the field application of the new tools, while providing trainees with practical hands-on experience in field research linked to disease control.

Starting in 1991, TDR also began experimenting with time-limited task forces, through which it could respond to the need for rapid solutions to disease control problems.

The plot thickens

Overall, this period can be seen retrospectively as a transition from a pre-1985 vision of disease control as a war between man and microbes with TDR as a think-tank for devising the necessary tactical weapons to a more mature realization that research targets cannot be simplistically isolated – in terms of individual parasites, for example – from the web of interrelated factors in which they are suspended. And in that web, people – their cultures, quirks, desires, needs – were beginning to be seen as central to any action aimed at lightening their suffering from disease (Box 5). To have any chance of long-term impact, such action, be it research or control, would have to be multipurpose, multidirectional (i.e. horizontal *and* vertical) and multidisciplinary, and be conducted through networks of interlinked groups crossing social, cultural, geographical – and, of course, disease – borders.

For TDR, this *matrix* approach has meant pulling down or making more permeable the walls separating its different compartments or components (see above, *Compartments and components*, p. 1). And it has called for scientists to pool their hitherto cloistered interests to produce results pertinent to several diseases and disciplines (Box 6).

Making every penny count

As noted by the World Bank in its 1993 analysis of *Global Economic Prospects and the Developing Countries,* "the aid 'pie' at the end of the Cold War is limited at a time when new claimants... have appeared".

TDR's response to a more competitive, less stable funding environment and to increasingly tight budgetary constraints has taken two directions: a greater emphasis on short- and medium- vs. long-term targets, corresponding to a tendency among the donor community as a whole to favour quick returns on time-limited investment, and a greater emphasis on activities likely to have a rapid impact. As described above (*From the field and back,* p. 5), TDR has begun to shift its focus and make tentative changes to its internal working environment so as to deliver research products more quickly to the field, without,

Box 5: Politics, progress and parasites: elements of change

Among the determinants of change affecting TDR's operating environment, three have in recent years become particularly critical to attempts to study and control tropical diseases: political change, physical manipulation of the environment in the name of development or "progress" and the uncanny ability of microbial populations to resist chemical attack:

Political unrest

Wars, civil disturbances and famines disrupt the life of a community, cripple its health services and offer an ideal terrain for epidemic outbreaks of tropical diseases, particularly malaria, African trypanosomiasis and leishmaniasis (as have occurred in Afghanistan, Cambodia, Chad, Somalia, Sudan, Uganda and Zaire, to mention only a few recent examples) or for the spread of diseases hitherto held in check (such as malaria and leishmaniasis in southern areas of the former Soviet Union).

Development dilemmas

Deforestation can pave the way for the spread of leishmaniasis and malaria. Dams can set the scene for onchocerciasis, schistosomiasis, malaria and guinea-worm. These and other human inroads into fragile ecosystems often pose a dilemma to developers: how to reconcile the often life-saving benefits of "progress" with the long-term risk of increased disease it may carry. The dilemma is most acutely illustrated by the proliferation of man-made water impoundments in the Sahel: they are often desperately needed to relieve starving communities, but offer ideal breeding grounds for schistosomes.

Parasite resistance to drugs

One of TDR's main drives in its search for new chemotherapeutic agents or combination regimens or health communication strategies to improve people's use of drugs is the need to keep at least one step ahead of a parasite's ability to acquire resistance to drugs. Parasites that multiply rapidly in their human hosts, such as those that cause malaria, leishmaniasis, African trypanosomiasis and Chagas disease, are likely to develop the genetic mutations associated with drug resistance more quickly than those with a more leisurely life-cycle, such as those responsible for schistosomiasis, lymphatic filariasis, onchocerciasis and leprosy.

AIDS could also contribute to drug resistance: chemotherapy usually kills enough microbes to allow host immune defences to cope with the rest, but people with depressed immunity because of AIDS might not be able to cope with even small numbers of microbes, which may therefore survive a chemotherapeutic onslaught. Such drug resistance is theoretically most likely to occur in HIV-positive individuals infected with leishmaniasis or leprosy.

With malaria, however, because of its lethal potential in inadequately treated patients, drug resistance offers the most alarming challenge to product developers: newer drugs, like mefloquine and halofantrine, have already begun to show diminished efficacy only a few years after their introduction, vs. the three or four decades it took for chloroquine to lose its efficacy in many malarious areas of the world. The prospects for even newer antimalarials, like some artemisinin derivatives currently in trials, are not auspicious.

BOX 6: Dismantling walls

Over the past three years, TDR has begun to draw from all its components the expertise needed to tackle problems that span the interests of several sectors or disciplines.

Scientists previously working under separate disease-oriented steering committees have joined forces, for example, on topics related to:

- *vulnerability – physiological*, as of children, pregnant women and the elderly (bringing together the interests of Steering Committees on the social sciences, epidemiology, malaria, Chagas disease and leishmaniasis); *economic, social and occupational*, as of women, children and migrants (social sciences and epidemiology); *geographical*, as of populations living in the African savannah, the Amazon forest, and areas of the Sahel or major cities of Brazil (onchocerciasis, malaria, schistosomiasis and leishmaniasis).

Other TDR teams have also recently formed around topics related to population groups, such as:

- *the sick child*, presenting an opportunity for common action on acute respiratory infection, diarrhoeal diseases, measles and malaria;
- *children of school age*, involving schistosomiasis and other helminthic diseases;
- *women*, involving social sciences, leprosy, chronic filariasis, onchocercal dermatitis and malaria.

TDR steering committees have also begun to work together on groups of diseases related by **causative agent**, such as:

- *the mycobacterial diseases* – leprosy and tuberculosis, for which an immunology steering committee, IMMYC, and a chemotherapy steering committee, THEMYC, were created in 1992;
- *the trypanosomatid diseases*—African trypanosomiasis, Chagas disease and leishmaniasis, for which an *integrated chemotherapy* steering committee, I-CHEM, was created in 1991;
- *the helminthic diseases* – schistosomiasis and other helminthic diseases, for which the concurrent use of the proven antischistosomiasis drug praziquantel and the antihelminthic albendazole is being tested in field trials;

or by **research focus**, such as:

- *drug development*, for which the Product Development Unit (see p. 7) was created;
- *applied field research*, involving the new Epidemiology and Field Research Unit and the Social and Economic Research Steering Committee (see p. 7).

Breaking down barriers has also meant closer collaboration between TDR and other groups working in areas related to tropical diseases:

- within or involving WHO, notably, the following divisions or programmes: Control of Tropical Diseases (CTD), Communicable Diseases (CDS) and the Programme on Vaccine Development (PVD) which it manages, Drug Management and Policies (DMP), Diarrhoeal and Acute Respiratory Disease Control (CDR), Family Health (FHE), AIDS (GPA), Development of Human Resources for Health (HRH), Health Education (HED), Health Learning Materials (HLM), Community Water Supply (CWS), Research Development and Research Training in Human Reproduction (HRP), Epidemiological Surveillance and Health Situation and Trend Assessment (HST), the Onchocerciasis Control Programme in West Africa (OCP), Prevention of Blindness (PBL), Planning Coordination and Cooperation (PCO), Secretariat Committee on Research involving Human Subjects (SCRIHS) and Strengthening of Health Services (SHS);
- outside WHO but within the United Nations system, notably: the United Nations Development Programme (UNDP), the United Nations Environment Programme (UNEP) and the United Nations Children's Fund (UNICEF);
- outside the United Nations system, notably: in the United States, the Rockefeller Foundation, the Edna McConnell Clark Foundation, the MacArthur Foundation; in Canada, the International Development Research Centre; in the United Kingdom, the Wellcome Trust and the Medical Research Council; in Brazil, the National Council of Scientific and Technological Development (CNPq); in India, the Indian Council of Medical Research (ICMR); in South-East Asia, the Tropical Medicine and Public Health Project (TROPMED).

TDR is also venturing increasingly into areas and topics where tropical diseases are only one of many health-related concerns, including: *the environment* (with WHO's Division of Environmental Health, UNEP, the Swedish Agency for Research Cooperation with Developing Countries, the Rockefeller Foundation and the Asian Development Bank; *education and communications* (with WHO's Division of Health Education and Office of Information), *health research* (with WHO's Health Systems Research and Development Unit and, more especially, the newly formed Council on Health Research for Development); *the sick child* (with WHO's Division of Diarrhoeal and Acute Respiratory Disease Control and with UNICEF); and *women* (with WHO's Division of Family Health).

however, abandoning longer-term objectives. It has also begun to identify priority research targets and to rank these priorities so as to favour those most likely to have a visible impact.

TDR's new priorities

In response partly to financial constraints and partly to its overall shift of emphasis towards field application of research outcomes, in 1992 TDR selected priority targets for each of the diseases within its mandate (Annex 2). This was followed, early in 1993, by a ranking of TDR's research goals according to six criteria: (1) need, in relation to disease burden and the degree to which the need is already satisfied by existing resources; (2) potential impact on disease, taking into account cost-effectiveness, affordability, acceptability – political, social, cultural and environmental – and the expected useful life of the research outcome; (3) scientific opportunity and feasibility; (4) expected time needed for development; (5) TDR's specific advantage for achieving a given goal; (6) cost of development. The resulting rank of an activity does not reflect the proportion of available resources to be allotted to that activity but simply provides a possible cut-off point – selected in relation to available funds – below which activities would receive no funding.

Looking at activities across the research spectrum, the highest scores go to applied field research, followed closely by product research and development, with strategic research trailing at a distance – a result not altogether unexpected since applied field research and product research and development activities concern tools and techniques whose development is close to successful completion, no longer requires costly initial

Box 7:
Changes in TDR's scientific environment

Several advances in science and technology are of relevance to TDR's objectives. They include, *in basic research*:

- the ability to manipulate the genomes of an increasingly wide range of organisms in order to selectively inactivate certain genes or introduce foreign genes;
- new methods, derived from human genome projects, for characterizing and sequencing large segments of DNA;
- a vast amount of new information from cellular and developmental biology using as models the insect *Drosophila melanogaster* and the roundworm *Caenorhabditis elegans*;
- advances in the dissection of the immune system through identification and cloning of lymphokines and functional characterization of immune cell populations.

In product research and development, several trends are pertinent to TDR's concerns:

- rapidly rising costs of drug and vaccine development;
- a tendency to more complex, time-consuming regulatory procedures, with increasing demand for data from field trials for marketing approval;
- the proliferation of national control authorities in developing countries;
- the growing evidence of extensive genetic homology between parasites and their human hosts, raising the possibility that drugs used for certain human diseases, such as cancer, could have anti-parasite activity;
- the tendency of the pharmaceutical and biotechnology industries to use several approaches to rational drug development (such as random peptide synthesis, anti-sense oligonucleotides, carbohydrate-mediated receptor blocking, lipid analogues of second messengers).

In applied field research, new analytical techniques and computer programmes are making it easier for epidemiologists and social scientists to handle large amounts of quantitative and qualitative data and identify problems common to many countries with tropical diseases. Use of these new assets is making it easier to devise common approaches to disease problems and to evaluate the efficacy of large-scale interventions.

Box 8:
Other actors

Among other actors in tropical disease research, those of the *public sector*—international and national research councils and multilateral or bilateral foundations and agencies—have in recent years been increasingly constrained by declining financial resources. The result has been a general move to consolidation of resources (such as Norway's recent melting down of its three research councils into a single council), a greater pooling of resources among different agencies on specific collaborative initiatives (TDR and the Rockefeller Foundation's joint partnership grants, for example) and a more focused definition of respective roles (such as UNICEF and UNDP leaning more heavily on their operational strengths and WHO more on its technical, norm-setting know-how).

In the private sector, funding of tropical disease research, particularly for long-term initiatives, has on the whole shown a gradual decline over the past decade among private foundations and programmes, compared with public sector institutions. United States foundations, in particular, are likely to focus increasingly on domestic "fourth world" problems of the country's growing underprivileged class. In private industry, only a few leading pharmaceutical companies now have development programmes for drugs for tropical diseases, a trend that reflects a growing concentration of firms in large conglomerates, product lines based more strictly on commercial interests and a consequently declining incentive to invest in markets with limited purchasing power.

development and therefore scores highly on three of the six criteria (3, 4 and 6) used for ranking.

The top three among the 21 priority activities for each group of products are as follows (see Annex 3 for complete scores of all activities):

- for drugs

  first: product research and development in malaria;

  equal second: applied field research in malaria, schistosomiasis and filariasis;

  equal third: product research and development in filariasis and leishmaniasis;

- for vaccines

  first: product research and development in leishmaniasis;

  equal second: product research and development and strategic research in malaria;

  third: strategic research in leishmaniasis;

- for diagnostic technology

  first: applied field research in leishmaniasis;

  equal second: applied field research in schistosomiasis and product research and development in filariasis;

- for vector control agents

  first, second and third: applied field research in Chagas disease, malaria and African trypanosomiasis, respectively.

SECTION 3: TAKING STOCK: TDR'S SPECIAL ROLE

Around the middle of the last decade, TDR entered a new phase of its existence with the realization that its mandate, its goals, its conception of research and its structure formed too monolithic a system to have a major impact on the tropical diseases. Over the next eight years, small, partial changes were made to TDR's working system so as to make it more open and responsive to "life out there" – the diseases and the people living and dying with them, the rapidly evolving world of science and technology, the changing political and economic scene – and therefore more likely to have an impact on the diseases. These changes were outlined in Section 2.

Today, in May 1993, with TDR poised to break with its, albeit rich and fruitful, early years and enter a bolder, more dynamic period, it is perhaps a good time to take stock of its strengths, weaknesses and its potential for playing a unique role in the health research arena.

A global perspective

Strengths

As part of the United Nations system, TDR enjoys two major assets: a world view of the tropical disease scene and the standing conferred by a lack of partisan or profit-making motivation. These assets explain in large measure TDR's rapid success in creating an international network of over 5,000 scientists, which gives it access to a broad range of expertise and scientific disciplines.

This network, especially its ramifications built up in developing countries through its research capability strengthening activities and its FIELDLINCS programme, now serves several critical functions, namely, as a means of:

- channelling information from the field to key research "nodes" and the secretariat in Geneva;
- linking research training with ongoing field projects (through the FIELDLINCS programme);
- planning multicentre studies sharing a common protocol;
- organizing projects or longer-term initiatives involving several countries or regions;
- fostering partnerships pertinent to research goals and topics – North-South, South-North, South-South or North-North;
- facilitating the transfer of technology and knowledge;
- identifying and consolidating the product development potential of developing countries.

From its global vantage point, TDR is also well placed to keep track of advances in science, technology and development. Indeed, through its influential role as global coordinator of research on tropical diseases, TDR often acts as an influential broker in research activities to which it may not be a major financial contributor. And through its WHO connection, TDR has ready access to programmes and units working in related fields (Box 6) and most importantly – with its new focus on the field and on national disease control programmes – to WHO's 185 Member States.

Weaknesses

A global operation like TDR can encounter irksome constraints, such as the logistic and administrative difficulties of managing projects involving several partners in several countries, each with its own legal, regulatory barriers.

Being part of an international civil service system also has its drawbacks, such as the existence of multiple checkpoints in project management and an elaborate staff recruitment process. And although WHO relieves TDR of much of the administrative drudgery involved in running an international programme, including payroll, office logistics, etc., it also imposes a number of time-consuming tasks (documentation, meetings, etc.) that are not always seen as critical to TDR's specific goals.

A "special" status

Strengths

As a *special* programme, run by WHO but sponsored by the UNDP and the World Bank and beholden to its governing body, the Joint Coordinating Board (JCB), TDR has a certain financial and administrative autonomy that makes for adaptability and responsiveness to change and saves it from much of the bureaucratic ponderousness common to large institutions. Nor can TDR become too mired in the self-centredness to which many of these institutions succumb: its two major bodies – the JCB and its Scientific and Technical Advisory Committee (STAC), which guides the JCB in its decisions affecting research – are largely made up of experts from outside the United Nations system and act as an open window to and from the world at large.

Weaknesses

As a special programme, TDR is sufficiently flexible to offer donors and other collaborators a means of fulfilling their aspirations. Yet, at the same time, its very status as a special programme deprives it of an assured regular income commensurate with these aspirations : having to compete for funds on "the open market", TDR has constantly to trim its goals, however achievable, to its relatively modest means.

Research management

Strengths

In two respects, TDR's research management policy contributes to its flexibility and responsiveness:

First, through its various committees, primarily its steering committees, TDR has direct, continuous contact with some 150 outside experts covering the full spectrum of research. With about a quarter of their members being replaced each year, the composition of these committees can be easily tailored to meet specific needs.

Second, TDR funds research mainly on a short-term, project-by-project basis rather than through long-term support of collaborative centres: in this way, it has been able to rapidly terminate unproductive projects and switch funds to more promising research activities.

Weaknesses

Despite the recent increase in the number of its units or steering committees spanning several research topics, TDR's steering committees are still mostly devoted to single diseases or topics. This compartmentalization has several drawbacks:

- since each committee manages research over the entire research spectrum – strategic research, product research and development, applied field research – its expertise is often spread too thinly to reach the "critical mass" necessary for the management of top-quality research in each individual area;
- for certain research topics, expertise represented in one committee may be duplicated by the same expertise in another committee;
- committees tend to focus too strongly on problems related to a single disease and may by-pass solutions that could be more cost-effectively applied to several diseases;
- compartmentalization limits cross-fertilization of ideas across research topics, and the concerted setting of research priorities and allocation of resources.

A further weakness of TDR's research management system up to now has been the almost total reliance of its steering committees on outside investigators to propose research projects: if no suitable proposal is submitted, an important research need may remain unsatisfied. Moreover, since they meet only once or twice a year, steering committees cannot respond quickly to new research opportunities and needs, nor can they provide continuous technical and administrative follow-up of research projects being funded.

TDR's comparative advantage

All in all, TDR's strengths, mentioned above, give it certain advantages over other actors on the development scene (Box 8):

- *Unlike national research councils,* TDR has an international research network and a global vantage point from which to identify unmet research needs and to plan and carry through international research projects or programmes that uniquely fill those needs.
- *Unlike bilateral funding agencies,* TDR mounts projects that combine research and research training, that involve, simultaneously, individual scientists, research groups, institutions and disease control programmes, and that cover several countries or regions.

- *Unlike private foundations and agencies,* TDR has the international backing and base, and the organizational and financial staying power to see large-scale projects through to their completion.
- *Unlike private industry,* TDR can follow-up on product development leads that may require a heavy investment in time, work and manpower without a strong guarantee of a commercially acceptable return on the investment.

SECTION 4: "A NEW WORLD TO EXPLORE"

Every innovation comes about through a combination of pre-existing elements...Often, the new combination seems interesting... by virtue of its form alone.... By playing with the new form to produce a new configuration at a higher level [of development], a new system emerges...a new world to explore...This process of emergence is at work in biology... René Thom, French mathematician.[5]

* * *

Section 1, above, (pp. 1-3) described the "pre-existing" elements of TDR's system, as it was set up at the start of the programme in 1975 and functioned up to the mid-1980s (Fig. 4).

Section 2 (pp. 5-14) outlined the transitional period from the mid-1980s to the present (May 1993), during which TDR's research focus shifted towards the field and the realities of disease control and its priorities towards research outcomes with a strong potential for impact on disease. To cater for this new focus and the new priorities, during this period TDR began experimenting with the elements of its system to produce the beginnings of a matrix resting on three main areas of research interest: strategic research, product research and development and applied field research.

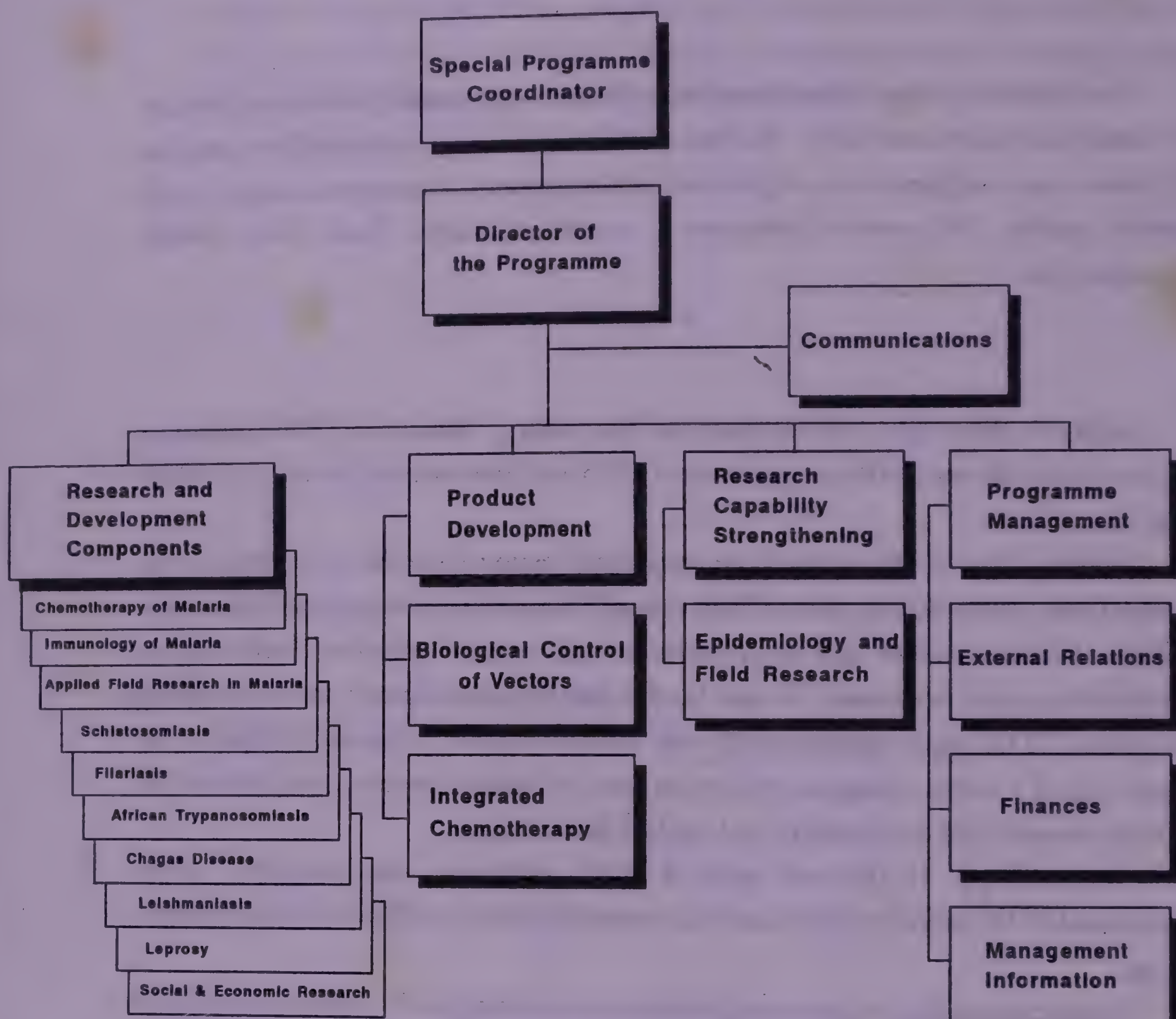
Section 3 (pp. 15-18) took stock of TDR's weaknesses and strengths – a still transitional TDR, looking to the future but structurally not very different from its original set-up.

This section outlines recommendations for a new strategy and a correspondingly new configuration of TDR's working parts that consolidate into a coherent whole most of the changes begun tentatively eight years ago. They have been worked out over the past year through a *prospective thematic review* of the scientific "directions" of TDR. The review process involved consultation with representatives of many interested groups, including JCB members and observers, TDR committee members and WHO officials and experts. In March 1993, the STAC, in the light of the review's conclusions and the different scenarios it proposed, made recommendations for consideration by the 16th session of the JCB. If these recommendations are accepted, TDR's activities will, starting from 1 January 1994, be organized along the following lines (Fig. 5):

- ***All TDR's activities*** would continue to be administered under the two main headings of research (or research and development) and research capability strengthening, and would remain targeted to the original diseases, but operationally the work carried out within these two administrative areas would be more closely interlinked and more mutually supportive;
- ***Research capability strengthening*** activities would continue to be managed by a single steering committee (the *Research Strengthening Group*), at least for the 1994-95 biennium;

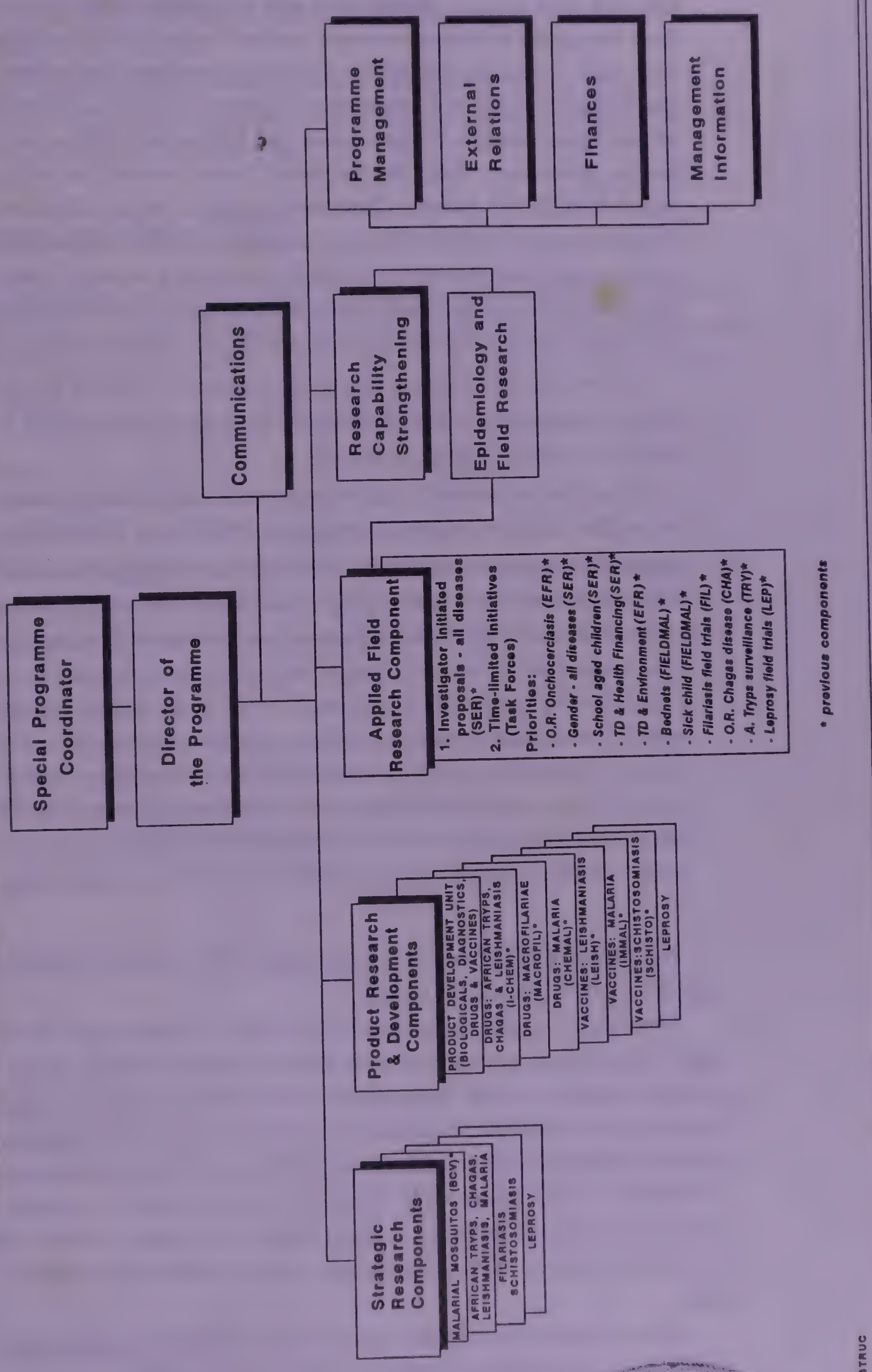
[5]from an essay on "The problem of innovation," Symposium, Encyclopaedia Universalis, 1985, pp. 81-82.

Fig. 4
Current Organization of the TDR Programme Secretariat



- *Research (research and development)* would fall into three main areas: strategic research, product research and development, and applied field research;
- *Strategic research* would employ the latest tools and advances of basic science to explore basic disease mechanisms, such as host-parasite relations and parasite biology, in order to achieve its *strategic* goal of producing radically new solutions that could, even in the long term, strengthen disease control. It would be managed by three Steering Committees concerned, respectively, with malarial mosquitos; protozoa – notably those associated with African trypanosomiasis, Chagas disease, leishmaniasis and malaria; and helminths – notably those associated with filariasis (lymphatic filariasis and onchocerciasis) and schistosomiasis. Strategic research activities relating to leprosy would continue to be managed by TDR's leprosy component, which since 1992 collaborates with WHO's Tuberculosis Programme through two mycobacterial disease steering committees, one concerned with immunology (IMMYC), the other with chemotherapy (THEMYC).

Fig. 5
Recommended Organization of the TDR Programme Secretariat from 1994



- *Product research and development* would select from the leads and prototype tools stemming from strategic research those with the greatest potential and would take them through the development process up to and beyond the Phase III (large clinical trials) stage. It would be managed by six steering committees, each concerned with a specific area of research and development on drugs and vaccines, as follows: drugs for African trypanosomiasis, Chagas disease and leishmaniasis (the current I-CHEM Steering Committee); drugs for the filarial diseases, notably macrofilaricides (the current MACROFIL Steering Committee); drugs for malaria (the current Malaria Chemotherapy or CHEMAL Steering Committee, modified to deal only with drugs); vaccines against leishmaniasis (a modified Leishmaniasis Steering Committee); vaccines against malaria (a modified Malaria Immunology or IMMAL Steering Committee); vaccines against schistosomiasis (a modified Schistosomiasis Steering Committee).

  The Product Development Unit would continue to handle a few (up to eight) high-priority products, including those used for diagnosis, and generally facilitate the work of the six new steering committees.

  Research on vaccines and drugs for leprosy would continue to be managed through the mycobacterial disease steering committees IMMYC and THEMYC, respectively.

- *Applied field research* would seek to identify the health problems and needs of communities and disease control programmes with a view to determining the best, most cost-effective ways of reaching affected communities with solutions most likely to be accepted and to have the strongest impact on disease. It would be managed by a single steering committee, which would "serve" all the diseases targeted by TDR research. Its work would encompass field research currently managed by the Social and Economic Research Steering Committee (SER), the Epidemiology and Field Research Unit (EFR), the Applied Field Research in Malaria Steering Committee (FIELDMAL) and other TDR steering committees. The Applied Field Research Steering Committee would in addition organize short-term task force initiatives on specific priority topics.

* * *

Not all the problems that the recommended TDR structure would encounter or engender can be foreseen at the outset.

Some critics fear that the orientation of TDR's activities by goals or research area might be disconcerting to scientists more used to a disease-by-disease approach; or that problems related to a specific disease may be overlooked by too great an emphasis on the broad view. These concerns are to some extent addressed by the STAC's suggested creation of a *disease coordinator* for each of the individual diseases: this staff member would protect "the interests" of the disease under his or her wing and serve as a contact point for communication and coordination on issues related to the disease, not only within TDR but especially between TDR and its partners in the scientific and development communities.

A more general concern is that with ever tighter financial constraints and a resulting emphasis on goals, priorities and targets, TDR might lock itself into a closed system with little room for discovery. As discoveries are inherently unexpected, they cannot be planned

for. They must, though, be allowed for. And TDR can do this by giving its networks of scientists the freedom to submit their own ideas and their own proposals for what they see as potentially exciting research.

But, in the last analysis, possible problems should *not* be a barrier to action. For if change can be dealt with, so can problems, as they arise. And change is certainly what TDR has learned to cope with in recent years.

A pivotal role for TDR?

Innovation, to return to René Thom, "is destabilizing by nature, to the extent that it has a social impact..." This possible effect, however, should be offset by the greater potential for creativity and interaction with the outside world of a programme functioning more as a living organism than as an accumulation of single cells.

If, as is likely, the new structure would represent a "higher level" of organizational development, TDR would without any doubt be better equipped to play a strong, even pivotal, role in a global effort to improve the health of the underprivileged people of the world. Indeed, in the course of the prospective thematic review that culminated in the recommended new strategy and structure of TDR, the idea of creating a global partnership or agenda to augment and coordinate the world's resources for research on tropical diseases was mooted as one step towards "a new vision of global cooperation for the next century[6]".

[6]Human Development Report 1992, UNDP p. 10

Annex 1: Products of TDR-supported research

(from TDR's 11th Programme Report)

The first two columns of this table indicate potential manufactured products for disease diagnosis, treatment or control to which TDR has contributed. Like the product table of the previous report, the present table does not include *techniques*, unless they represent manufacturable items.

The column "in preclinical development" indicates potential products which have been undergoing *laboratory* evaluation for safety and biological efficacy, as a prerequisite for clinical and field trials.

The column "in clinical or field trial" indicates potential products which have been undergoing evaluation *in humans* to show safety and efficacy, together with diagnostics and vector control tools which have been under field trial.

Products are listed under "in disease control use" if they are now used in disease diagnosis, treatment or control. Products are designated by the year of first appearance in each category. Bracketed years indicate developments which took place outside TDR.

Product	In preclinical development	In clinical or field trial	In disease control use
MALARIA			
Drugs			
Artemisinin and derivatives	1984	1992	1994
Chloroquine resistance reversers	1988		
Mefloquine and mefloquine combinations	(1977)	1979	1984
Tumor necrosis factor antagonist for severe malaria		1991	
Vaccines			
Plasmodium falciparum asexual blood-stage vaccine	1977	1992	
P. falciparum sporozoite vaccine		1986	
P. vivax sporozoite vaccine		1989	
P. falciparum transmission blocking vaccine	1989		
Diagnostics			
DNA and RNA probes to monitor drug resistance	1989		
Microtest kit for measuring *P. falciparum* sensitivity to antimalarial drugs			1985
Field tests for measuring antimalarial drugs in biological fluids		1987	
DNA probes for detection of *P. falciparum* and *P. vivax* in blood		1987	
Vector Control			
Diagnostic monoclonal antibody-based (Zavala) test for species-specific detection of sporozoites in mosquitos		1986	1989
Insecticide-impregnated bednets		1991	
Other			
Portable incubator			1986
SCHISTOSOMIASIS			
Drugs			
Praziquantel drug combinations for multidrug therapy	1990	1991	
Vaccines			
Recombinant DNA schistosomiasis vaccine	1989		
Diagnostics			
Morbidity assessment by ultrasonography		1989	

Product	In preclinical development	In clinical or field trial	In disease control use
Diagnostic urine filtration technique		1980	1983
Immunodiagnostic assays	1992		
FILARIASIS			
Drugs			
Ivermectin for onchocerciasis	(1978)	1982	1987
Ivermectin for lymphatic filariasis		1988	
CGI 18041 for onchocerciasis/lymphatic filariasis	1989		
CGP 6140 for onchocerciasis		1987	
UMF 078 for onchocerciasis/lymphatic filariasis	1989		
Diagnostics			
DNA probes for *Brugia malayi* infective larvae			1989
DNA probes for *Onchocerca volvulus*		1989	
Monoclonal antibody for *Brugia malayi*			1989
Antigen assays for routine serodiagnosis of onchocerciasis and lymphatic filariasis	1989		
DNA probes for detection of microfiliaria in blood		1989	
Vector Control			
B. Sphaericus		1992	
AFRICAN TRYPANOSOMIASIS			
Drugs			
Eflornithine	1978	1986	1990
Eflornithine combination therapy	(1985)	1989	
Diagnostics			
Antigen-ELISA	(1988)	1989	
Card Agglutination test for trypanosomiasis (CATT)	1978	1980	1983
Diagnostics (cont.)			
Procyclic agglutination test for trypanosomiasis (PATT)	1989		
Miniature anion-exchange centrifugation technique	1979	1981	1984
Vector Control			
Insecticide impregnated screens	1984	1989	1989
Monoconical insecticide-impregnated traps	1984	1989	1989
Pyramidal tsetse fly trap	1984	1981	1981
CHAGAS DISEASE			
Drugs			
Allopurinol for chronic disease	1986	1992	
Diagnostics			
Agglutination test for blood bank screening			1989

Product	In preclinical development	In clinical or field trial	In disease control use
Serodiagnostic test using synthetic peptides		1992	
Vector Control			
Fumigant canister			1990
Insecticidal paints			1990
Triatomine detection box			1990
Crystal violet/sodium ascorbate to kill parasites in infected blood in blood banks		1989	
LEISHMANIASIS			
Drugs			
New regimen for antimony compounds		1979	1984
Allopurinol combination therapy		1989	
Gamma-interferon + antimony compounds	1984	1988	
Amidazoles	1982	1989	
Paromomycin ointment	(1950)	1990	
Antitubulin compounds	1989		
Lipid associated amphotericin B	(1988)	1992	
Vaccines			
Killed leishmania vaccine, New World	(1960)	1992	
Killed leishmania vaccine, Old World	(1960)	1991	
Recombinant vaccine for New World *(Leishmania mexicana)*	1992		
Recombinant vaccine for Old World leishmaniasis	1992		
Diagnostics			
Direct agglutination test (DAT)	1983	1992	
Dot-ELISA		1992	
Standard leishmania skin test antigen		1991	
LEPROSY			
Drugs			
Clarithromycin	1991		
Combined drug regimen for PB leprosy – WHO/MDT			1982
Combined drug regimens for MB leprosy – WHO/MDT			1982
Fluoroquinolones	1985	1991	
Minocycline	1991		
Ofloxacin/rifampicin combination		1991	
Vaccines			
Heat-killed *Mycobacterium leprae* vaccine		1983	
Diagnostics			
PCR to detect small numbers (<100) *M. leprae* organisms	1991		
Native/recombinant and synthetic antigens for diagnostics	1989		

Product	In preclinical development	In clinical or field trial	In disease control use
BIOLOGICAL CONTROL OF VECTORS			
Vector Control			
Bacillus brevis	1989		
B. sphaericus	1983	1990	
B. thuringiensis H-14	1976	1980	1982
Clostridium bifermentans	1990		
Competitive snails	1978	1985	
Lagenidium giganteum	1982	1986	
Larvivorous fish	1975	1975	1975
Novel vector control organism by genetic manipulation	1985		

Annex 2: Targets of TDR-supported research*
(from TDR's 11th Programme Report)

MALARIA

Strategic research

- Systems developed for the genetic manipulation of malaria parasites.
- *In vitro* parasite cell lines established for research towards second-generation vaccines and for drug screening.
- Factors responsible for disease and protective immunity in humans, and for parasite development in mosquitos, identified.
- The genetic basis of drug resistance clarified, and leads to combating resistance being pursued.
- Novel methods of rendering mosquitos resistant to malaria parasites being pursued.
- Biological larvicides under development to survive and multiply in upper layers of water, releasing toxins fatal to mosquito larvae.

Product development

By 1994:

- Clinical efficacy tested of anti-TNF monoclonals, of artemether and of arteether, in the treatment of childhood cerebral malaria.
- Artemether registered in France.

By 1995:

- Efficacy of insecticide-treated bednets in preventing childhood malaria mortality assessed in three representative African areas.
- Arteether ready for registration.
- Ten new drug leads identified.
- At least one new first-line drug candidate or drug combination in clinical trial as an inexpensive replacement for chloroquine.
- Phase II trials of transmission-blocking vaccine complete. Phase II trials started.
- Efficacy of SPf66 synthetic malaria vaccine determined in Tanzanian children.

By 1997:

- Two further drug candidates in clinical development as replacements for chloroquine.

By 2002:

- Phase I-III trials completed on most of the 15-20 current leading vaccine antigen candidates.

Applied field research

By 1994:

- Strategy available for the diagnosis and treatment of childhood malaria, especially in Africa, as part of an integrated strategy for sick children.

By 1994:

- Control strategies identified for urban malaria in Africa.

By 1995:

- Simple, cheap and rapid means of diagnosing malaria and detecting antimalarials in urine available, to detect those *not* needing treatment, to save countries' much needed supplies of drugs.

By 1995:

- Community-based strategies identified for rapid and effective treatment, especially in Africa.

By 1995:

- Methods identified to reduce malaria deaths in pregnant women.

By 1997:

- Revised strategies available for surveillance, to enable rapid response to potential outbreaks of severe and complicated malaria.
- Methods identified for overcoming factors that prevent women from seeking malaria treatment, especially among pregnant women, unmarried adolescents, and mothers.
- Rapid assessment methods for epidemiological surveillance of malaria tested.

SCHISTOSOMIASIS

Strategic research

- Host-vector relationship better understood, especially with regard to skin penetration, worm pairing, migration in the body, egg deposition and the pathophysiology of granuloma formation.
- *In vitro* cell lines developed for drug and vaccine research.

Product development

By 1994:

- Phase III trials completed on the dual

(continued)

* *These targets were those provisionally agreed by December 1992; they are to be reviewed and updated at meetings to be held in 1993*

administration to schoolchildren of albendazole and praziquantel.

By 2000:

- Phase I-III trials completed of at least five promising vaccine antigens, either alone or in combination.

Applied field research

By 1995:

- The best means of introducing praziquantel identified.
- Rapid methods for identifying communities where schistosomiasis is highly endemic tested.
- Strategy identified for increasing women's understanding of disease risk factors, and for increasing women's use of preventive and therapeutic measures.
- Novel immunodiagnostic assays in field trials.

By 1996:

- Feasibility assessed of using praziquantel combined with other drugs in schoolchildren.

By 1997:

- Feasibility assessed of incorporating information on schistosomiasis into general health promotion for schoolchildren.

FILARIASIS

Strategic research

- Application made of the genetic map, now under development, of the nematode *Caenorhabditis elegans*, to topics including the mechanisms of ivermectin resistance, and the host-parasite relationship, in particular, worm pairing in the human host.
- *In vitro* cell lines for drug screening and vaccine research developed.
- In lymphatic filariasis, the use of ultrasound and other techniques for imaging the lymphatic system, as major aids for early diagnosis and treatment – and for understanding the development of pathology – established.

Product development

By 1995:

- Serological test for lymphatic filariasis available.
- The efficacy of *Bacillus sphaericus* in the control of filarial vectors assessed.
- Serological antibody-based test to detect reinvasion of areas by disease-causing *Onchocerca* parasites available for operational use.

By 1997:

- Macrofilaricide registered for human use.

By 1998:

- Simple serological test kit for the diagnosis of lymphatic filariasis available for operational use.

Applied field research on lymphatic filariasis

By 1994:

- The incidence, duration and social and economic costs of acute attacks assessed.
- Stigmatizing genital problems caused by the disease in women assessed.

By 1995:

- Social, economic and public health importance of the disease assessed.

By 1996:

- Ivermectin tested as a macrofilaricide, in combination with diethylcarbamazine (DEC).
- The effect of ivermectin against chronic disease assessed.
- The effect of ivermectin in morbidity and transmission control assessed.

Applied field research on onchocerciasis

By 1993:

- Inexpensive methods of identifying high-risk communities developed.

By 1994:

- Most cost-effective ways of distributing ivermectin to villages and their inhabitants identified.

By 1995:

- Best method of eliminating onchocerciasis as a public health problem in Latin America identified.

By 1995:

- The scale of onchocercal skin disease in women assessed, and whether ivermectin can reduce it.

By 1997:

- A new macrofilaricide registered for human use.

LEPROSY

Strategic research

- Complete *Mycobacterium leprae* genome map used to improve understanding of the pathogenesis of disease, particularly of the mechanisms of nerve damage and protective immunity.

Product development

By 1995:

- Feasibility tested of shorter, more cost-effective treatment regimens.

By 1998:

- Highly cost-effective drug regimens, involving intermittent administration of few doses, available.

By 2000:

- Phase III trials of first-generation vaccines completed.

Applied field research

By 1995:

- Methods selected to improve community awareness of leprosy, involve communities in its control, and reduce social stigma.
- Cost-effective approaches to disability and rehabilitation identified.
- Methods identified to reduce the risks of leprosy among pregnant women.

AFRICAN TRYPANOSOMIASIS

Strategic research

- Mechanisms responsible for pathogenesis identified.
- Common non-variant surface antigens identified for vaccine research.
- Use made of advances in the understanding of immune regulation, and in genetic manipulation of immune mechanisms (involving cytokines and immune cell deletion techniques), to probe the pathogenesis of brain damage, and to identify new approaches to treatment and prevention.

Product development

By 1994:

- Large-scale field tests of an antigen-based diagnostic test completed.

By 1995:

- A facility available in a developing country for producing eflornithine.

By 1997:

- Antigen-based diagnostic test kit available for routine distribution to control programmes.
- At least two new drugs in clinical trials.

By 2000:

- At least one new drug registered for the treatment of *gambiense* or *rhodesiense* disease.

Applied field research

By 1995:

- Community-based surveillance strategies selected for testing.

By 1998:

- Studies validating a community-based surveillance strategy completed in different cultural and epidemiological settings.

CHAGAS DISEASE

Strategic research

- Use made of advances in understanding of immune regulation and in genetic manipulation of immune mechanisms (involving cytokines and immune cell deletion techniques) to probe the pathogenesis of heart damage and to identify new approaches to treatment and prevention.
- Attenuated and/or growth-limited strains developed for vaccine research.

Product development

By 1994:

- Diagnostic kits with molecularly defined antigens available for blood screening; introduction into disease control begun.

By 1995:

- Preclinical or clinical development under way of at least two new drugs.

By 1996:

- Simple test based on the polymerase chain reaction (PCR) available for screening transfusion blood for Chagas disease parasites, as well as – for example – hepatitis virus, HIV, and malaria parasites.

By 2000:

- At least one new drug registered for human use.

Applied field research

By 1994:

- Optimal combination of vector control measures — use of insecticides (sprayed, applied in paints or delivered from canisters), improvement of housing and health education — identified and applied in rural and periurban areas.
- Measures identified to improve the surveillance of Chagas disease in women during pregnancy and of infants after delivery.

By 1995:

- Most effective strategy identified for the prevention of parasite transmission by blood transfusion, making use of the diagnostic kits described above and other methods.

LEISHMANIASIS

Strategic research

- Genes responsible for pathogenesis identified.
- Attenuated and/or growth-limited strains developed for vaccine research. *(continued)*
- Use made of advances in understanding of

immune regulation and in genetic manipulation of immune mechanisms (involving cytokines and immune cell deletion techniques) to probe the pathogenesis of mucocutaneous lesions and to identify new approaches to treatment and prevention.

Product development

By 1994:

- Phase III trials under way of at least one vaccine candidate for cutaneous leishmaniasis.
- Phase III trials of amphotericin B lipid complexes completed, and one product registered.

By 1995:

- Clinical trials under way of at least three new drugs.
- Simple diagnostic kit available for visceral leishmaniasis.

By 1996:

- Clinical trials under way of at least one vaccine candidate against visceral leishmaniasis.

By 1998:

- Vaccine registered for use against cutaneous leishmaniasis.

By 2000:

- At least one drug registered for the treatment of visceral and mucocutaneous leishmaniasis.
- At least one vaccine registered for use against visceral leishmaniasis.

Applied field research

By 1995:

- The most effective vector control method identified.
- Strategies identified to improve women's understanding of leishmaniasis, and to improve children's compliance with treatment.
- Studies completed to show whether women suffering from cutaneous leishmaniasis have difficulties obtaining treatment.

Annex 3: A ranking of TDR-supported research activities

DRUGS

	STRATEGIC RESEARCH Score	Rank	PRODUCT DEVELOPMENT Score	Rank	APPLIED FIELD RESEARCH Score	Rank
MAL	1.8	10	1.2	1	1.3	2
SCH	2.2	16	-		1.3	2
FIL	2.0	14	1.4	5	1.3	2
ATR	2.2	16	1.6	9	1.9	13
CHA	2.1	15	1.5	7	-	
LEISH	1.8	10	1.4	5	-	
LEPR	--		1.8	10	1.5	7

VACCINES

	STRATEGIC RESEARCH Score	Rank	PRODUCT DEVELOPMENT Score	Rank	APPLIED FIELD RESEARCH
MAL	1.5	2	1.5	2	-
SCH	2.3	8	1.8	5	-
FIL	2.3	8	-		-
ATR	2.6	11	--		-
CHA	2.2	7	--		-
LEISH	1.7	4	1.3	1	-
LEPR	2.4	10	2.0	6	-

DIAGNOSIS

	STRATEGIC RESEARCH Score	Rank	PRODUCT DEVELOPMENT Score	Rank	APPLIED FIELD RESEARCH Score	Rank
MAL	--		1.9	11	1.5	5
SCH	-		1.7	8	1.3	2
FIL	-		1.3	2	1.7	8
ATR	-		1.6	6	1.6	6
CHA	-		1.9	11	1.4	4
LEISH	2	13	1.8	10	1.2	1
LEPR	2	13	2.1	15	-	

VECTOR CONTROL

	STRATEGIC RESEARCH Score	Rank	PRODUCT DEVELOPMENT Score	Rank	APPLIED FIELD RESEARCH Score	Rank
MAL	1.9	5	--		1.3	2
SCH	--		--		-	
FIL	-		1.9	5	-	
ATR	-		-		1.7	3
CHA	--		-		1.2	1
LEISH	-		--		1.8	4